LETTER TO THE EDITOR

Hypoperfusion, Mitochondria Failure, Oxidative Stress, and Alzheimer Disease

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Alzheimer disease (AD) and cerebrovascular accidents (CVA) are the two leading causes of age-related dementia. The risk of AD, stroke, and CVA are known to increase at comparable rates with age. Recent advances on several fronts suggest that the vascular risk factors, which are linked to cerebrovascular disease and stroke in the elderly, significantly increase the risk of AD. Although some vascular lesions (eg, cerebral amyloid angiopathy, endothelial degeneration, and periventricular white matter lesions) are evident in most AD cases, fully one third of these cases will exhibit cerebral infarcts. Despite the interpretation of pathological evidence, longitudinal clinical studies suggest that stroke and AD occur in tandem more often than by chance alone. Strokes often occur in patients with AD and have been linked to the pathogenesis of dementia. Nevertheless, the nature of this relationship remains largely unexplored. Irrespective of the ultimate pathogenic mechanism, these findings suggest that managing vascular disease is important in the treatment and prevention of AD or mixed dementia.

Increasing evidence supports the notion that the underlying mechanism responsible for CVA is also responsible for AD-related dementia. The implicated pathogenesis, which is primarily responsible for both disease processes, seems to involve chronic hypoperfusion. Hypoperfusion appears to induce chronic oxidative damage in tissues and cells, largely due to the generation of reactive oxygen and reactive nitrogen species (ROS and RNS, respectively). Any condition, which outpaces the capacity of endogenous redox systems to neutralize such toxic intermediates, leads to a system imbalance or to major compensatory adjustments that rebalance the system. This new redox state is generally referred to as "*oxidative stress*" and is associated with other age-related degenerative disorders, such as atherosclerosis, ischemia/reperfusion, and rheumatic disorders. Chronic injury stimuli can also induce hypoperfusion in the microcirculation of vulnerable brain regions.

Many common disease risk factors may underlie and play key roles in the development of cardiovascular, cerebrovascular, and neurodegenerative diseases. For example, it has been widely accepted that hypercholesterolemia is a risk factor for the development of cardiovascular and cerebrovascular disease as well as AD. Vascular insufficiency/hypoperfusion also is considered to be a pathogenic factor in the development of AD. Further, the positive relationship between cerebrovascular diseases, such as stroke and especially cerebrovascular atherosclerosis, indicates that the latter may also be linked to the pathogenesis of AD. In addition, ischemia/reperfusion induce chronic hypoxic conditions, which cause the formation of a large amount of oxygen free radicals, which also appear to be a key factor in the development of these diseases. In support of this notion, new evidence has immerged, which indicates that continuous formation of oxygen free radicals induces cellular damage and decreases antioxidant defenses. The vascular endothelium, neurons, and glia are all able to synthesize and release ROS and vasoactive substances in response to certain stimuli, especially that of chronic hypoxia/hypoperfusion. The contribution of these substances to the pathogenesis of CVA and AD is extremely important. The role of hypoperfusion, as a key factor for vascular lesion formation and which causes oxidative stress, appears to be widely accepted as an initiator of AD. This idea is based on a positive correlation between AD and cardiovascular diseases. ROS are generated at sites of injury and/or inflammation.

The vascular endothelium, which regulates the passage of macromolecules and circulating cells from the blood to tissues, is a major target of oxidant stress and plays a critical role in the pathogenesis of several vascular diseases. Specifically, accumulated oxidative stress increases vascular endothelial permeability and promotes leukocyte adhesion, followed by alterations in endothelial signal transduction and redox-regulated transcription factors. We hypothesize that the cellular and molecular

mechanisms, by which hypoperfusion-induced ROS accumulation impairs endothelial barrier function and promotes leukocyte adhesion, induce alterations in normal vascular function and result in the development of AD. Sustained hypoperfusion with concomitant oxidative stress to brain tissues could also stimulate secondary damage via the overexpression of inducible and neuronal specific nitric oxide synthase (NOS: iNOS and nNOS, respectively) and endothelin-1 (ET-1) in brain cells. It is possible that continuous production of oxidative stress products, such as peroxynitrite accumulation (via the overexpression of the iNOS and/or nNOS), may appear to be secondary and accelerating factors for damage and for compromising the blood-brain barrier (BBB) in hypoxia/hypoperfusion or AD.

One of the main effects of chronic hypoperfusion-induced vascular abnormalities in AD appears to be tissue oxygen deficiency. Recent evidence supports a critical role for chronic cerebral hypoperfusion in the development of cognitive impairments such as AD. When seen together with AD, accumulating evidence reveals that a greater fraction of oxygen is removed from the vasculature in AD patients as compared to non-AD controls. Therefore, low vascular blood flow, a prominent feature of the brain during chronic hypoxia/hypoperfusion, may be a priming (or initiating) factor in the development and maturation of AD. These metabolic defects are present before the development of AD symptoms in apolipoprotein E (ApoE) $\varepsilon 4$ homozygote patients. De la Torre proposes that advancing age with a comorbid condition, such as a vascular risk factor that further decreases cerebral perfusion, promotes a critically attained threshold of cerebral hypoperfusion (CATCH). With time, CATCH induces brain capillary degeneration and suboptimal delivery of energy substrates to neuronal tissue. Because glucose is the main fuel of brain cells, its impaired delivery, together with a deficient delivery of oxygen, compromises neuronal stability because the supply for aerobic glycolysis fails to meet the brain tissue demand. The outcome of CATCH is a metabolic cascade that involves, among other things, mitochondrial dysfunction, oxidative stress, decreased production of adenosine triphosphate (ATP) and other reducing equivalents of (NADH/NADPH), increased calcium entry, abnormal protein synthesis, cell ionic pump deficiency, signal transduction defects, and neurotransmission failure. These events contribute to the progressive cognitive decline characteristic of patients with AD, as well as regional anatomic pathology, consisting of synaptic loss, senile plaque formation (SP), neurofibrillary tangles (NFT), tissue atrophy, vasculopathy, and neurodegeneration. CATCH identifies the clinical heterogenic pattern, which characterizes AD because it provides compelling evidence that any of a multitude of different etiopathophysiologic vascular risk factors, in the presence of advancing age, may lead to AD. We hypothesize that, taken together with vascular endothelial cells (EC) and smooth muscle cell (SMC) abnormalities induced by hypoperfusion, these are key factors in impaired tissue oxygen delivery and therefore appear to be main reason for the development of AD.

Importantly, the reduced energy production found in hypoperfusion may lead to energy failure. This failure ultimately manifests itself as damage to mitochondrial ultrastructure in the different brain cellular compartments. Ultrastructural impairments include the formation of a large number of nonmature or the so-called "young," electron-dense "hypoxic" mitochondria and overproliferation of abnormal mitochondrial DNA (mtDNA). Additionally, these mitochondrial abnormalities are found to coexist with increased redox metal activity, overexpression of lipid peroxidation markers, and with RNA oxidation. This oxidative stress occurs within various cellular compartments, most notably in neurons and vascular EC, and is responsible for atherosclerotic damage. Nevertheless, vulnerable neurons and associated glial cells show mtDNA deletions and overexpression of oxidative stress markers only in regions proximal to the damaged vessels which also show the same pattern of mitochondrial abnormality and oxidative stress marker overexpression. This evidence strongly indicates that it is chronic hypoperfusion that induces lesions and causes the accumulation of the oxidative stress products seen in AD. Determining the mechanisms, which underlie these imbalances, may provide crucial information in the development of new, more effective therapies for the treatment of cerebrovascular diseases, including AD. Therefore, any pharmacological intervention, directed at correcting the chronic hypoperfusion state, would possibly change the natural course of development of dementing neurodegeneration.

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